

REMARKS

In response to the Office Action mailed August 25, 2006, Applicant has amended claims 1, 6-9, 12-13, 22, 45, 54, 57-58, and 67, canceled claims 2, 4, 11, 20-21, 47, 49, 56, 65, and 90-94, and added new claim 125. Support for all the above amendments may be found throughout the specification as originally filed, for example in original claims 2, 4, 11, 20, 47, 49, 56 and 65 and Example 1. No new matter has been added. The above amendments are not to be construed as acquiescence with regard to the Examiner's rejections and are made without prejudice to prosecution of any subject matter removed or modified by this amendment in a related divisional, continuation or continuation-in-part application. Following the amendments, claims 1, 6-10, 12-19, 22-31, 33-38, 41-46, 51-55, 57-64, 66-76, 78-83, 86-89, and 125 are pending and under consideration in the application. Claims 3, 5, 32, 39-40, 48, 50, 77, 84-85, and 95-124 are withdrawn from consideration. Favorable reconsideration of the subject application is respectfully requested in view of the above amendments and the following remarks.

Priority

Applicant notes that a certified copy of the 2003-092898 priority application is being submitted concurrently in the parent application (U.S. Application No. 10/684,141). As such, further to MPEP § 201.14(b) II, the requirement under 35 U.S.C. § 119(b) has been satisfied.

Claim Rejections – 35 U.S.C. § 112, second paragraph (indefiniteness)

Claims 1, 2, 4, 6-15, 20-31, 33-38, 41-47, 49, 51-60, 65-76, 78-83 and 86-94 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. In particular, the Action asserts that the claims do not recite any positive steps rendering the method steps unclear. The Action also asserts that claims 22 and 67 as worded indicate that DNA polymerase comprises a mismatched base. Since DNA polymerases do not consist of bases, the Action contends that the claims are unclear. Further, the Action asserts that certain claims lack antecedent basis.

Without acquiescing to the rejection and solely to advance prosecution, Applicant has amended independent claims 1 and 45 to positively recite method steps and has canceled claim 90. Further, claims 22 and 67 have been amended to recite “one mismatched base being greater by at least one than that provided by a wild type of the DNA polymerase.” Applicant submits that the claims as amended and new claim 125 positively recite method steps, have sufficient antecedent basis and would be readily understood by the skilled artisan. As such, Applicant submits that the claims as amended satisfy the requirements under 35 U.S.C. § 112, second paragraph, and respectfully request reconsideration of the claims and withdrawal of the rejection.

Claim Rejections – 35 U.S.C. § 112, first paragraph (enablement)

Claims 1, 2, 4, 6-19, 22-31, 33-38, 41-47, 49, 51-64, 67-76, 78-83, and 86-94 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly lacking enablement. In particular, the Action asserts that the specification, while being enabling for methods using yeast DNA polymerase δ with a higher error-prone frequency than wild-type DNA polymerase δ and wherein the polymerase provides mismatched bases at a frequency of 10^{-6} or greater, does not reasonably provide enablement for methods using yeast DNA polymerase δ with a lower error-prone frequency than wild-type DNA polymerase δ , methods using prokaryotic DNA polymerase δ , or methods using polymerases with an error frequency less than 10^{-6} .

Applicant respectfully traverses the rejection on the following grounds. As an initial matter, Applicant notes that claims 1, 6-9, 12-13, 22, 45, 54, 57-58, and 67 have been amended and claims 2, 4, 11, 20-21, 47, 56, 65, and 90-94 have been canceled without acquiescence or prejudice. Applicant reserves the right to prosecute any subject matter modified or removed by this amendment in a related application. Applicant provides the following remarks as they may apply to the claims as amended.

Applicant submits that one skilled in the art would clearly understand from the specification as filed how to make and use in the present methods, polymerases other than yeast DNA polymerase δ , such as prokaryotic DNA polymerase δ . For instance, the specification as filed highlights that DNA polymerases having a proofreading function present in gram positive

bacteria, gram negative bacteria, and eukaryotic organisms all have an *ExoI* motif that plays a role in 3'→5' exonuclease activity and has an influence on the accuracy of the proofreading function (see for example, page 41, lines 12-17). Moreover, DNA polymerases having a proofreading function have well-conserved aspartic acid and glutamic acid regions that are regarded as the proofreading function active site (see for example, page 42, line 31 to page 43, line 3). As such, Applicant submits that the skilled artisan would readily understand from the specification as filed how to modify DNA polymerases other than yeast DNA polymerases (*e.g.*, prokaryotic DNA polymerases) to appropriately alter the proofreading function for use in the claimed methods. Further, and as discussed in more detail below, Applicant submits that doing so would require only routine experimentation on the part of the skilled artisan.

A specification is presumed to be enabling and the U.S. Patent and Trademark Office (PTO) has the burden of establishing a *prima facie* case of lack of enablement. *See, In re Angstadt*, 190 U.S.P.Q. 214, 219 (C.C.P.A. 1976); *In re Marzocchi*, 169 U.S.P.Q. 367, 369-370 (C.C.P.A. 1971). To make a *prima facie* case of lack of enablement, the PTO must come forward with *reasons*, supported by the record as a whole, showing why the specification fails to enable one of skill in the art to make and use the claimed invention. *In re Angstadt*, 190 U.S.P.Q. 214, 219 (C.C.P.A. 1976). The mere fact that some experimentation is necessary does not negate enablement as long as undue experimentation is not required. *See* M.P.E.P. § 608.01(p).

The burden is on the PTO to establish that experimentation would be undue, *Angstadt*, 190 U.S.P.Q. at 219, taking into consideration factors that have been articulated for determining whether the disclosure is enabling. *In re Wands*, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). Contrary to the assertions outlined in the Action, Applicant submits that the amount of experimentation which may be required to practice the present invention does not rise to the level of being *undue* experimentation, as defined by the Court in *Wands*.

An important aspect of the Court's decision in *Wands* is its finding that the nature of the technology pertinent to the Wands invention (monoclonal antibody production) permitted a *broad* definition of the term "experiment." The Court found that an "experiment" in the monoclonal antibody art consisted of the entire attempt to make a monoclonal antibody against a

particular antigen. As described by the Court, the process entailed, “immunizing animals, fusing lymphocytes from the immunized animals with myeloma cells to make hybridomas, cloning the hybridomas, and screening for antibodies produced by the hybridomas for the desired characteristics.” 8 U.S.P.Q. 2d at 1407. Thus, *Wands* supports the conclusion that in a complex field such as monoclonal antibody production, the entire attempt to achieve the desired result, from beginning to end, constitutes *one* experiment.

According to the Court, repetition of this whole experiment more than once does not constitute undue experimentation. As the Court indicated, practitioners in the art would be prepared to screen negative hybridomas in order to find a hybridoma making the desired antibody. 8 U.S.P.Q.2d at 1406. Thus, the fact that some aspects of the experiment as a whole will yield negative results does not mandate finding that the amount of experimentation to achieve a positive result is undue.

Applied to the instant application, the generation of mutant polymerases (*e.g.*, POL3 mutants) and further screening to identify those mutants that have a higher proofreading function as compared to wild-type, may require some experimentation. However, viewed in the light of *Wands*, this experimentation cannot be considered “undue,” even allowing for the possibility of encountering negative results along the path to positive results. Furthermore, relevant techniques are known in the art and referred to by the present specification which provides extensive guidance to allow the skilled artisan to generate mutants and screen them for the appropriate proofreading activity (see *e.g.*, Example 1 and references cited therein). Moreover, Applicant submits that appropriate techniques in the art which provide guidance to allow the skilled artisan to generate mutants and screen them for the appropriate proofreading activity are, in fact, described in the Kokoska *et al.* reference cited by the Action under 35 U.S.C. § 102.

Accordingly, Applicant submits that the quantity of experimentation necessary is not excessive given the amount of permissible routine screening that would be involved, as described above. As also discussed above, more than ample amounts of direction or guidance are presented with regard to polymerase mutants and to determination of whether any such mutants possesses altered proofreading activity, which can be detected readily through the use of

methodologies known to the art and disclosed in the specification. Particularly where, as here, the level of skill in the art is high, with practitioners typically holding a Ph.D. or the equivalent, Applicant submits that the skilled person can readily generate polymerase mutants and further, ascertain whether or not a given mutant possesses the desired altered proofreading activity, given the instant specification and teaching in the prior art.

Notwithstanding the above remarks, Applicant has amended independent claims 1 and 45 to specifically recite “increasing the error-prone frequency of at least one DNA polymerase of the cell to higher than that of a wild type DNA polymerase.” This amendment is made without acquiescence or prejudice and solely to advance prosecution.

In view of the above remarks and amendments, Applicant submits that the claims are enabled and respectfully request that the rejection under 35 U.S.C. § 112, first paragraph be withdrawn.

Claim Rejections – 35 U.S.C. § 102

Claims 1, 2, 4, 6-14, 16, 17, 20, 21, 23-25, 28-31, 33-38, 41, 42, 45-47, 49, 51-59, 61, 65-70, 73-76, 78-83, 86, 87, and 90-94 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Morrison *et al.* (EMBO J., 1993). In particular, the Action asserts that the *pol3-01* mutant strains described by Morrison *et al.* have wild-type POL2 and POL1, that the mutant polymerase provides a mismatch mutation of at least 10^{-6} , that the mutant strain grew substantially as well as the wild-type strain and that the POL3 detects errors in the daughter strand of a replication fork and mutants thereof would therefore provide a different number of errors in each strand. Accordingly, the Action alleges that the reference anticipates the presently claimed invention.

Similarly, claims 1, 2, 4, 6, 9-14, 16, 17, 20-25, 28-31, 33-38, 41-47, 49, 51, 54-59, 61, 62, 73-76, 78-83, and 86-94 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Kokoska *et al.* (Mol. Cell. Biol. 2000). Specifically, the Action asserts that Kokoska *et al.* teach yeast strains comprising temperature sensitive mutants of the POL3 gene which are involved in proofreading gene replication errors. The Action further asserts that the *pol3-01* mutant strains described by Kokoska *et al.* have wild-type POL2 and POL1, that the

mutant polymerase provides a mismatch mutation at a 20-fold difference from wild-type, that the mutant strain grew substantially as well as the wild-type strain and that the POL3 detects errors in the daughter strand of a replication fork and therefore the mutants thereof would result in a different number of errors in the daughter strand as compared to the parent strand. Accordingly, the Action alleges that the reference anticipates the presently claimed invention.

Applicant respectfully traverses the rejections. Applicant notes that claims 1, 6-9, 12-13, 22, 45, 54, 57-58, and 67 have been amended and claims 2, 4, 11, 20-21, 47, 56, 65, and 90-94 have been canceled. Applicant provides the following comments as they may apply to the claims as amended, including new claim 125.

Applicant submits that neither Morrison *et al.* nor Kokoska *et al.* disclose or suggest the claimed methods. In particular, these references do not teach or suggest a method for regulating a conversion rate of a hereditary trait of a cell, comprising increasing the error-prone frequency of at least one DNA polymerase of the cell to higher than that of a wild type DNA polymerase, wherein at least two kinds of DNA polymerases playing a role in the gene replication are present, and wherein the at least two kinds of DNA polymerases have heterogeneous error-prone frequencies, and wherein conversion of the yeast cell confers high temperature resistance to the cell.

In particular, Morrison *et al.* merely create a *pol3-01* mutant and examine the relationship between *pol3-01* and *pms*. Morrison *et al.* fail to disclose a method wherein conversion of the yeast cell confers high temperature resistance to the cell. Similarly, Kokoska *et al.* merely teach random mutagenesis of the entire POL3 gene and examine various mutator alleles. Kokoska *et al.* do not describe a method for regulating a conversion rate of a hereditary trait of a cell, comprising increasing the error-prone frequency of at least one DNA polymerase of the cell to higher than that of a wild type DNA polymerase, wherein at least two kinds of DNA polymerases playing a role in the gene replication are present, and wherein the at least two kinds of DNA polymerases have heterogeneous error-prone frequencies, and wherein conversion of the yeast cell confers high temperature resistance to the cell.

In view of the above amendments and remarks, Applicant submits that the claims as amended are not anticipated by the cited references. Reconsideration of the claims and withdrawal of the rejections are respectfully requested.

Double Patenting

Claims 45, 90, and 91-94 stand rejected under statutory-type double patenting under 35 U.S.C. § 101. The Action asserts that, in light of the election of yeast cells as a species the scope of the claims 45 and 90 is allegedly identical in that they produce a yeast cell, which is an organism, using the same method steps. The Action asserts that the same is true for claims 91-94.

The claims also stand provisionally rejected under 35 U.S.C. § 101 as claiming the same invention as that of the claims in co-pending Application No. 10/810,486.

Without acquiescing to the rejection and solely to advance prosecution, Applicant has canceled claims 90-94 and amended claims 1 and 45 as noted above. Further, Applicant has canceled claims 1-109 in co-pending Application No. 10/684,141. These amendments are made without prejudice to prosecution of any subject matter removed or modified by the amendments in a related divisional, continuation or continuation-in-part application. As such, Applicant submits that the above rejections under 35 U.S.C. § 101 have been obviated and may be properly withdrawn.

Provisional Rejection under Obviousness-type Double Patenting

Claims 44 and 89 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting over claims 39 and 79 of co-pending Application No. 10/684,141.

Without acquiescing to the rejection, Applicant respectfully requests that the Examiner hold the rejection in abeyance until the claims in the instant application are determined to be allowable. Applicant will consider filing a terminal disclaimer at that time.

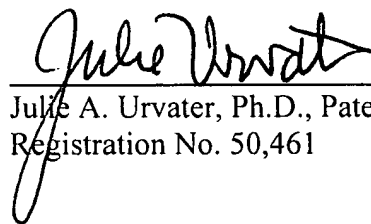
Application No. 10/810,486
Reply to Office Action dated August 25, 2006

Applicant respectfully submits that all of the claims remaining in the application are now believed to be in condition for allowance. Favorable consideration and a Notice of Allowance are earnestly solicited.

The Director is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

Respectfully submitted,

SEED Intellectual Property Law Group PLLC

A handwritten signature in black ink, appearing to read "Julie Urvater", is written over a horizontal line.

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